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Safety and Tolerability of a Modified TIMI-14 Protocol in AMI Patients: A Pilot Study

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Aim of the study was to evaluate the safety and tolerability of a modified combination of thrombolysis plus glycoprotein IIb/IIIa receptor inhibitors in AMI patients versus a TIMI-14 protocol.

132 hospitalised patients within 4 h from onset of symptoms were randomised (double blind) in two groups. Group Immediately (66 patients) received thrombolytic treatment (50 mg rtPA) according to TIMI-14 study and standard treatment with glycoprotein IIb/IIIa receptor inhibitors. Group After (66 patients) received thrombolytic treatment (50 mg rtPA in 30 min) and after 30 min from starting thrombolysis received glycoprotein IIb/IIIa receptor inhibitors.

Group Immediately: 51 patients showed rapid reperfusion as confirmed by coronarography performed after 12–72 h. Group After: 60 patients showed rapid reperfusion as confirmed by coronarography after 12–72 h. Side effects were similar in both groups. Patients receiving a modified protocol showed a favourable trend in incidence of reperfusion.

Our data suggest the possibility to use a modified protocol and show the feasibility, safety and tolerability of this different protocol in timing of combination of GP IIb/IIIa receptor inhibitors with thrombolysis in patients with AMI. The bleeding risk was similar in both groups. These very preliminary data suggest other and larger studies. *J Clin Basic Cardiol* 2002; 5: 193–6.

Key words: acute myocardial infarction, TIMI-14 trial, GP IIb/IIIa inhibitors

Thrombolytic treatment has demonstrated an important reduction of mortality (30 to 6.3 %) in patients thrombolysed within 6 hours from onset of symptoms [1]. The AMIs involving a large area of myocardium show a high mortality (20–25 %) [2] and these patients appear to receive a greater benefit by an aggressive treatment (primary or rescue PTCA) when thrombolysis is unsuccessful [3, 4]. Unfortunately, a quarter of patients show failure to lyse occlusive thrombi, reocclusion occurs in 10 % of patients, and incomplete reperfusion is present in 30 % [5, 6]. Because interventional laboratories are not available in all hospitals, and often, when they are available, they are not open 24 hours a day, other attempts to obtain reperfusion were used (rescue thrombolysis) with increased incidence of major bleeding [7]. The recent TIMI-14 trial showed that the combination of reduced-dose thrombolysis and abciximab determined an increase of patency at 90 min [8]. The aim of the study was to compare a TIMI-14 modified protocol versus TIMI-14 protocol in AMI patients and to verify safety and tolerability of the modified protocol.

Materials and Methods

Population

From June 2000 to April 2001, 325 patients were admitted consecutively to hospital with suspected acute MI.

Eligibility Criteria

Patients had to have a first episode of AMI, Killip class I–II, acceptable echocardiographic window and to be admitted and starting the treatment within 4 hours of the onset of symptoms (pain). On the ECG there had to be an ST elevation of > 1 mm in the peripheral leads and/or 2 mm in precordial leads, involving more than one lead, with concomitant alterations of the segmentary kinetics in the echocardiogram performed at entry. The basal creatine kinase (CK, CK-MB isoenzyme before thrombolysis) had to be within the normal range. There was no age limit. Informed consent was obtained from all patients.

Exclusion Criteria

Patients not suitable for thrombolysis, with left bundle branch block, a history of cardiomyopathy, or heart failure were excluded from the study.

Reperfusion Criteria

There had to be evidence of typical behaviour of the ST segment with rapid reduction, 50–70 % within 1 hour in 12 leads ECG monitoring, rapid regression of pain, an enzymatic (CK) peak within 12 hours of treatment, and early ventricular arrhythmias within 2 hours of the start of thrombolysis. The CK peak within 12 hours and rapid ST segment reduction in 12 lead ECG monitoring, were considered mandatory associated with one of the other reperfusion criteria.

AMI Classification

Acute MIs were classified according to the localisation of the alteration in segmental contractility in the echocardiogram performed at entry and according to the localisation of the alterations of the ST segment in the standard 12 lead ECG + V3R–V4R lead taken at entry before thrombolysis. All patients received our standard treatment with nitrates, heparin (according to TIMI-14 study) a bolus of 60 U/kg (maximum 4000 U) and infusion of 7 U/kg/min (maximum 800 U/h). For both groups, infusion was adjusted according to a normogram to a target activated partial thromboplastin time (aPTT) of 50–70 seconds, aspirin and, where possible, three doses of intravenous metoprolol 5 mg. The thrombolytic drug used was the recombinant tissue plasminogen activator (15 mg bolus, followed by infusion of 0.50 mg/kg up to 35 mg over 60 minutes) and the GP IIb/IIIa inhibitors used were abciximab (0.25 mg/kg bolus plus 10 mcg/min infusion for 12 hs), tirofiban (0.4 mcg/kg/min for 30 minutes plus 0.1 mcg/kg/min for 72 hs) and eptifibatide (180 mcg/kg bolus plus 2.0 mcg/kg min infusion for 72 hs).

Study Protocol

Patients suitable for thrombolysis received thrombolytic treatment, together aspirin, heparin as above reported and

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GP IIb/IIIa inhibitors immediately (according to TIMI-14 trial) or received thrombolytic treatment (50 mg rtPA in 30 min) and after 30 min from starting thrombolysis glycoprotein IIb/IIIa receptor inhibitors. The patients were randomised (double blind) in two groups: Group Immediately (66 patients) received thrombolytic treatment (50 mg rtPA) according to TIMI-14 study and standard treatment with glycoprotein IIb/IIIa receptor inhibitors (abciximab, tirofiban, eptifibatide). Group After (66 patients) received thrombolytic treatment (50 mg rtPA in 30 min) and after 30 min from starting thrombolysis glycoprotein IIb/IIIa receptor inhibitors (abciximab, tirofiban, eptifibatide) (Figure 1). All patients received heparin therapy according to TIMI-14 data and 160 mg aspirin. All patients who showed reperfusion after GP IIb/IIIa treatment (pain, ST segment resolution etc.) performed coronarography after 12–72 hours and PTCA/CABG where indicated. Patients without reperfusion signs were immediately referred to rescue PTCA/CABG. After starting thrombolysis, BP, HR, and ECG were monitored continuously. Blood CK levels were measured every 3 hours during the first 24 hours and then every 6 hours until normalisation, to determine the enzymatic peak (12 hours) and just after the randomisation (at entry) an echocardiogram was carried out. All the patients underwent a haemodynamic study (12–72 hs). PTCA/CABG were performed according to angiographic findings and left ventricular function. Patients enrolled in the study were regularly followed up as out-patients. Patients carried out echocardiographic examination before discharge and after 1 month from treatment when they underwent exercise test as PTCA protocol.

Statistical Analysis

Results are expressed as the mean \pm SD. Data were analysed by the two-tailed t-test to identify differences between the groups and ANOVA for repeated measures with Bonferroni correction for intra-group data. Nominal data were analysed

by the Chi-square test. $P < 0.05$ was assumed as statistically significant.

Results

132 consecutive patients meeting the entry criteria were included into the study (99 male; 33 female; mean age 59 ± 12 in Group After and 60 ± 13 in Group Immediately). Patients were randomised in two groups (double blind), with groups being similar for clinical data and risk factors (Table 1). Patients receiving GP IIb/IIIa inhibitors immediately and after thrombolysis who showed rapid non-invasive reperfusion in the early coronarography (12–72 hours) showed an IRA patency (TIMI-3 flow) corresponding to the classification of reperfusion based on non-invasive diagnosis. Group Immediately included 66 patients. Haemodynamic evaluation after 12–72 hours showed patency of IRA in 51 patients. These 51 patients showed rapid reperfusion (first 30–45 min) during infusion of the IIb/IIIa glycoprotein inhibitors treatment and thrombolytic drug administration.

Fifteen patients did not show any reperfusion and were sent to rescue PTCA. We decided to perform coronarography in this group 12–72 hours after the treatment to obtain the best stabilisation and to avoid the risks due to early mechanical procedure. Group After included 66 patients, all receiving 50 mg of rtPA (30 min) and GP IIb/IIIa inhibitors administration after 30 min from the starting of thrombolysis. Sixty patients showed rapid reperfusion during bolus of the glycoprotein IIb/IIIa inhibitors administration (4 ± 3 min). Haemodynamic evaluation after 12–72 hours showed patency of IRA in these 60 patients. The difference between two groups was significant ($p < 0.05$). Only six patients from Group After did not show reperfusion criteria and performed emergency coronarography and performed rescue PTCA. Heparin treatment was given according to TIMI-14 trial in both groups [8]. We observed 3 cases of side effects (major bleeding) in Group After: one mild grade pericardial bleeding remitted after heparin withdrawing, 1 gastrointestinal bleeding and 1 retroperitoneal bleeding, 31 cases of minor bleedings (16 from Group After and 15 from Group Immediately), four cases of blood transfusions were required. Four patients showed platelet reduction < 100.000 (2 cases in each group), 6 hours after the onset of abciximab treatment. Eight died during hospitalisation (3 from Group After and five from Group Immediately). Two patients who were thrombolysed late (> 6 hours) after the onset of symptoms and presenting a large anterior AMI, showed rapid reperfusion but died after 24 hours of cardiac rupture as confirmed by echocardiogram and pericardialcentesis (Group After), one patient died during PTCA. Two patients with 3 vessels disease died during

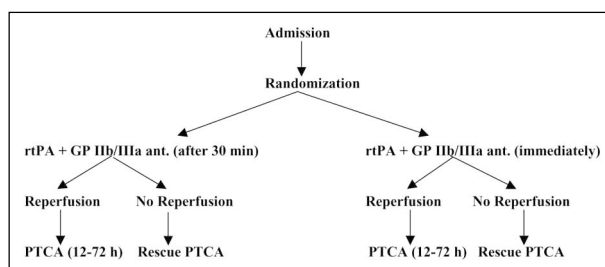


Figure 1. Protocol of the study

Table 1. Clinical data of the enrolled patients

	After	Immediately
Patients no	66	66
Sex M/F	49/17	50/16
Age	59 ± 12	60 ± 13
CK peak max (IU/l)	1787 ± 985	1895 ± 1080
CABG/PTCA	18/48	15/45
Ventricular tachycardia	48	42
Lown's class > 2	6	9
Beta-blockers	3	42
Hypertension	33	30
Diabetes	15	18
Hypercholesterolaemia	40	43
Smokers	25	29
Inferior AMI	39	36
Anterior AMI	24	27
Lateral AMI	3	3

Table 2. Results of the study

	After	Immediately
Patients no	66	66
Patency	60	51
No patency	5	15
Side effects		
Major bleeding	3	2
Minor bleeding	16	15
Platelet reduction	2	2
Mortality	3	5
Coronarography		
3 vessels	11	12
2 vessels	15	18
1 vessel	39	36
Restenosis	8	10
Stent	24	25
		ns

emergency surgery (Group Immediately), two patients during PTCA and 1 patient of irreversible heart failure due to re-AMI. Table 1 shows the clinical data and the results obtained from each group. Group Immediately showed 12 patients with 3-vessel, 18 patients with 2-vessel and 36 patients with one-vessel disease, one patient died before coronarography (Group After). The Group After showed 11 patients with 3-vessel, 15 patients with 2-vessel and 39 with one-vessel disease. The incidence of PTCA or CABG was similar in both groups. One month after treatment 18 patients (8 from Group After and 10 from Group Immediately) showed pain and electrocardiographic alteration recurrence either at rest or during exercise test, and the coronarography again performed showed restenosis in previously PTCA treated vessel. Endsystolic volume and ejection fraction did not show significant differences between the two groups (unshown data). All patients received aspirin and ticlopidine twice daily along with statins and the usual post-MI treatment (beta-blockers, nitrates, ACE-inhibitors etc.) Long-term follow-up and inclusion of larger population is ongoing. Only 49 patients received stent treatment (24 from Group After and 25 from Group Immediately).

Discussion

Limited success in the restoration of coronary blood flow and in the reduction of reocclusion in thrombolysis has been attributed to activation of platelets [9, 10]. After plaque rupture, a different set of factors is critical in the pathogenesis of thrombus formation: the degree of plaque rupture, the degree of stenosis and the physicochemical properties of the surface exposed. Authors showed that platelet deposition occurred with subsequent thrombus formation within 5–10 minutes [11]. The thrombus obstructing the infarct related artery in ST-elevation MI consists of multiple elements, including platelets, thrombin, and fibrin mesh. The dynamic interplay between factors promoting thrombosis versus those promoting thrombolysis is shifted in favour of thrombosis. Although thrombolytic agents target the fibrin mesh component of the thrombus, their use is associated with both heightened thrombin activity and platelet activation [12]. A transient, but significant increase of thrombin as a response to thrombolysis was shown. The increased thrombin levels are strongly related to the short-term outcome of thrombolysis [13]. Thrombin not only promotes further thrombus formation but is one of the most potent stimuli for activation of platelets [14]. In response to stimulation by thrombin, platelets express GP IIb/IIIa receptors, promoting cross-linking by ligands such as fibrinogen, providing a greater area for formation of the prothrombinase complex and additional thrombin formation. [15]. In addition, activation of platelets determine release of plasminogen activator inhibitor-1 (PAI-1) and vasoconstrictors substances [15]. Thus, the platelet-rich thrombus is not only more resistant to thrombolysis, but additional platelet activation after initially successful thrombolysis may promote reocclusion. From a mechanistic perspective, an antiplatelet agent used in combination with a thrombolytic drug not only offers the potential to enhance thrombolysis and to reduce the risk of reocclusion but permits this to be accomplished with reduced doses of thrombolytic agents and heparin. In fact, recent angiographic studies showed that a substantial portion of occlusive thrombi (previously thought to consist only of fibrin-rich 'red' clot) is made up of platelets (the so-called 'white' clot) [16]. The generation of thrombin and activation of platelets at the site of vascular injury frequently limits thrombolytic therapy. This thrombolytic resistance may be due to several mecha-

nisms: incomplete lysis of the clot because plasminogen activators act only on the portion of thrombi, presence of PAI-1 elaborated by platelets inhibiting the action of the thrombolytic drugs, and release of TXA₂, which causes vasoconstriction and may limit recanalization of IRA, exposition of clot-bound thrombin which can cleave fibrinogen to fibrin, thereby facilitating rethrombosis, and thrombolytic platelet-activating effect, leading to increased levels of platelet-activating factor [14]. Thus, fibrinolysis promotes platelet activation by creating conditions that trigger rethrombosis or reocclusion, or both. The binding of the GP IIb/IIIa receptor with fibrinogen or von Willebrand factor represents the final common pathway of clot formation. Blockade of these receptors results in profound suppression of platelet aggregation [17]. Recently, the combination of GP IIb/IIIa with thrombolysis showed an increase of reperfusion in patients with AMI [8, 18, 19]. In TIMI-14 the 50 mg dose of t-PA (15 mg bolus and 35 mg infusion over 60 min) achieved substantial improvement in TIMI grade 3 flow 77 % at 90 min as compared with 62 % for t-PA alone [8]. Overall patency at 90 min was achieved in 94 % of patients with the combination of abciximab plus t-PA as compared with 78 % for t-PA alone. An even greater difference was observed at 60 min when adding GP IIb/IIIa inhibition. Overall patency at only 60 min was achieved in 91 % of patients with the combination of abciximab and t-PA as compared with 70 % for t-PA. Myocardial perfusion as assessed by ST segment resolution was also significantly improved by the combination [20]. Major haemorrhage was similar among the t-PA plus abciximab and control groups, 6 % in each. In-hospital mortality was similar in all groups, ranging from 3 % to 5 %. One of the main concerns in considering combination therapy of a potent fibrinolytic agent and a potent antiplatelet agent is bleeding, in particular, intracranial haemorrhage [21]. The review of three randomised trials shows that GP IIb/IIIa inhibitors produce no increase in ICH [22]. Our data suggest the possibility of using a modified TIMI-14 protocol in patients with AMI. No patients had fatal intracranial bleeding and only two patients requested plasma transfusion. In addition, the patients receiving GP IIb/IIIa inhibitors after 30 min from thrombolysis showed a significant increase of reperfusion of IRA. The modified combination of therapy used in our patients allowed us to overcome thrombolytic resistance [23]. It is possible that this modified combination was able to lyse before the fibrin linked to clot and in this way allowed a better action of GP IIb/IIIa inhibitors to act on platelet rich thrombi. The most important results were the safety of this combination, the increase of patency need requires further investigations. We hypothesized that in patients receiving GP IIb/IIIa receptor antagonists after thrombolytic treatment (30 min), that thrombolysis determined incomplete lysis of the clot (only fibrin) and facilitated in this way the action of GP IIb/IIIa receptor antagonists on platelet rich thrombi. This is the first time that this different combination of GP IIb/IIIa receptor inhibitors plus thrombolysis was used in the setting of AMI [8]. Noteworthy was the high incidence of reperfusion in patients receiving this modified combination (60 patients), and the difference to TIMI-14 protocol was significant. Our data show a better and interesting incidence of IRA patency in comparison with TIMI-14 protocol. These very preliminary data suggest the possible use of this different combination in patients with AMI. We hypothesised that modified combined treatment could help us to overcome thrombolytic resistance and in this way to increase the incidence of reperfusion in AMI patients. This was exclusively a feasibility and tolerability study, which requires other investigations to confirm the favourable findings observed in our study.

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